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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on Sept. 22, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-77 is/are pending in the application.
Of the above, claim(s) 35-54 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-34 and 55-77 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Patent Application, PTO-152

SEE OFFICE ACTION ON THE FOLLOWING PAGES

Applicant's election without traverse of group I, claims 1-34 and 55-77 in Paper No. 5 is acknowledged.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 17-22,25-27,34,57,59,61,64,66,68,71 and 72 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass human embryos, fetuses, offspring and progeny and transgenic/chimeric human embryos, fetuses, offspring and progeny. Claim 34 reads on human differentiated cells in a human It is established Patent Office policy not to allow claims which read on humans, transgenic or otherwise. See 1077 OG 24, April 21, 1987. Applicant is suggested to amend these claims to read non-human.

Claims 1-34 and 55-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of cloning a mammal comprising inserting a differentiated mammalian cell or cell nucleus, a differentiated mammalian cell or cell nucleus wherein a DNA sequence is inserted, removed or modified, a differentiated CICM cell or cell nucleus, into an enucleated mammalian oocyte, activating the nuclear transfer unit, culturing the activated nuclear transfer unit to greater than the 2-cell stage and transferring the cultured nuclear transfer unit to a host mammal, fetuses, offspring, progeny, transgenic fetuses, transgenic offspring, transgenic progeny, a method of producing a CICM cell line

comprising inserting a differentiated mammalian cell or cell nucleus, or a differentiated mammalian cell or cell nucleus wherein a DNA sequence is inserted, removed or modified, into an enucleated mammalian oocyte, activating the nuclear transfer unit, culturing the activated nuclear transfer unit to greater than the 2-cell stage and culturing cells obtained from the nuclear transfer unit, a CICM cell line, differentiated cells, methods of making chimeras, chimeric embryos, chimeric fetuses, chimeric offspring and organs from the various offspring.

The claims are not enabled as the specification does not provide sufficient guidance on cloning a mammal by any of the methods claimed such the artisan could repeat the method and have a reasonable expectation of success at the time of filing in obtaining fetuses, offspring or progeny without undue experimentation. The nature of the art at the time of filing was that the cloning of a mammal, that is the production of a fully, developed mammal from a fully differentiated cell or from a nucleus of a fully differentiated cell was unlikely to be successful. At the time of filing, the art knew that the transfer of nuclei from differentiated adult cells into frog oocytes would result in the production of tadpoles, but not the differentiation to adult frogs (Wilmut et al, page 810, col. 2, parag. 2, lines 1-3). The art, however, had reported the development of mammals by the insertion of a nucleus from a totipotent embryonic cells into an enucleated oocyte (US Patent 4,994,384, col. 10, lines 4-10; Sims et al, page 6146, col. 2, parag. 1-3 and Campbell et al, page 65, col. 2, lines 3-11). Thus the artisan while being able at the time of filing to obtain guidance from the art on the production of mammals by the insertion of a nucleus from a totipotent embryonic cell into an enucleated oocyte, the artisan could not have found such guidance when the nucleus was from a fully differentiated cell. For this the artisan could only rely on the instant specification.

The specification provides working examples to show the development of chimeric an transgenic embryos and fetuses, but no production of a live birth. Example 1 demonstrates

the production of fibroblast cultures from fetal bovine and porcine tissues and from adult bovine tissue. Cells from each of these cultures were shown to take up and express the β-galactosidase gene. One cell line, CL-1, a fetal bovine fibroblast cell line, provided the donor nucleus for nuclear transfer experiments where transgenic fetal bovines. Example 2 demonstrates the production of CICM cells first producing a nuclear transfer unit by inserting the nucleus of a bovine fetal fibroblast (CL-1) into an enucleated oocyte and culturing the nuclear transfer unit . Disaggregation of the cultured NT's resulted in CICM cultures. Intact CICM cells were inserted into 8-16 cell embryos to produce chimeric fetal calves. Transgenic fetal calves were produced by removing the nucleus of a CICM cell and inserting it into an enucleated oocyte, as was done in example 1 with fetal fibroblasts. However none of these examples demonstrate the production of a live birth. This remains unpredictable, as even the more established methods where totipotent embryonic cell nuclei were used resulted in the loss of mammals during gestation (Campbell et al, page 65, col. 2, lines 5-10). Even post-filing art, employing a method similar to applicant's resulted in the birth of only one sheep, further demonstrating the unpredictability of the claimed method (Wilmut et al, page 812).

The production of chimeric animals is of itself lacking reproducibility. There are not guidelines provided in the specification for the production of a chimeric mammal such that the mammal has a use to the art. Chimeric mammals are unpredictable, as the contribution of the transferred cell or nucleus is not controllable. There is no method for regulating those portions of the mammal to which the transferred cell or nucleus contributes, nor is there a method for reproducibly making chimeric mammals that are the same. For example is mammal 1, the transferred cell or nucleus may contribute to the liver, and in mammal 2, it may contribute to the brain. There is no way to reproducibly ensure that the transferred cell or nucleus contributes the same in multiple mammals. Thus the production of chimeric mammals is unpredictable.

Further, there is no evidence of record that the transgenic or chimeric fetuses and mammals produced by the instantly disclosed method would result in mammal that would provide organs for transplantation. The transgene would need to be expressed sufficiently so that the organ would be immune from rejection for example. The showing of β-galactosidase expression is not sufficient to demonstrate transgene expression sufficient for transplantation. There is no correlation in the art or in the specification between levels of β-galactosidase expression and levels of transgene expression in general that affords a new use to mammalian embryos, fetuses, offspring or progeny. The specification at page 10, lines 9-21 and page 11, lines 7-18 discusses the uses of the mammals as organ donors. It is not clear how a mammal that does not express a transgene that alters the host-graft response will be useful as an organ donor. As for other uses, the specification fails to disclose other clear uses for the mammals and none are apparent. There is no evidence that the mammals made by the disclosed methods provide a patentable use. The question here is how would the artisan use the mammals made by the method?

The specification in particular has not provided a use for humans made by the disclosed methods. As the claims encompass both the making of humans and humans so made, the argument is proper. How and under what circumstances would humans be so made?

The unpredictability of the method as a whole lies in the need to convert a differentiated cell to a totipotent cells. As cells contain the same DNA complement. However, in differentiated tissues, not all DNA sequences are expressed. For example, a liver does not make rhodopsin and retinal cell structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development it, or its nucleus, must be reverted back to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. Applicant has not shown that the

method of cloning using transferred cell or nucleus demonstrated is sufficient for the production of fully developed mammals. The examples show the production of transgenic and chimeric bovine fetuses, but there is no demonstration that the activation method would active non-bovine nuclei. Further, the gene activation time for mammalian embryos may be critical for producing a fully differentiated mammal. Activation times were known in the art to vary: the mouse activates at the 2-cell stage, and human, cow and sheep activate around the 4 to 8 cell stage (Schultz et al, page 206, col. 2, parag. 2, lines 1-3). The activation time may be critical for the production of a fully developed mammal.

Thus for these reasons the claimed invention is not seen as enabled by the specification.

Claims 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 34 read on cells in an intact mammal or human. Thus it is confusing as to whether applicant is claiming cells in a mammal or human, or the mammal or human. It is suggested that applicant either claim the intact non-human mammal, or indicate that the cells are isolated.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-19,25-27,71-73,75 and 77 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by US Patent 5,057,420 issued October 15, 1991 ('420).

The claims are drawn to fetuses, offspring and progeny produced by claimed methods of cloning a mammal, and organs from the offspring. However, as claims 17-19,25-27,71-73,75 and 77 are product by process claims, a teaching of the same products obtained by a different method serves as anticipatory art against the instantly rejected claims.

'420 teaches bovine embryo, fetuses and offspring (col. 5-6, table 1). Claims 17-19,25027,71 and 72 do not distinguish the embryos, fetuses, offspring and progeny claimed from the embryos, fetuses and offspring taught by '420. The organs of the offspring are an inherent feature of the offspring, and are anticipated therefore by '420. Without a distinction which indicates a structural or functional difference between the claimed embryos, fetuses, offspring and progeny and those disclosed in '420, '420 clearly anticipates the claimed invention.

Claims 20-22,57,59,61,64,66,68,74 and 76 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hyttinen et al (1994) Bio/Technology 12, 606-608.

The claims are drawn to transgenic, chimeric and transgenic/chimeric fetuses, offspring and progeny produced by claimed methods of cloning a mammal, and organs from the offspring. However, as claims 20-22,57,59,61,64,66,68,74 and 76 are product by process claims, a teaching of the same products obtained by a different method serves as anticipatory art against the instantly rejected claims.

Hyttinen et al teach the production of transgenic and chimeric or mosaic bovine embryos, fetuses and calves (page 606, col. 2, parag. 2 to page 607, col. 2, lines 4). Claims 20-22,57,59,61,64,66 and 68 do not distinguish from the embryos, fetuses, offspring and progeny claimed from the embryos, fetuses and offspring taught by Hyttinen et al. The organs of the offspring are an inherent feature of the offspring, and are therefore anticipated by Hyttinen et al. Without a distinction which indicates a structural or functional difference

between the claimed embryos, fetuses, offspring and progeny and those disclosed in Hyttinen, Hyttinen clearly anticipates the claimed invention.

Claim 29 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sims et al (1993) Proced, Natl. Acad. Sci. 90, 6143-6147.

Claim 29 is drawn to a CICM cell line. However, as claim 29 is a product by process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the claim.

Sims et al teach the culture of ICM cells as cell lines 6-10 (page 6146, col. 1, parag. 2 and table 4). Claims 29 does not distinguish from the ICM cell line taught by Sims et al. Without a distinction which indicates a structural or functional difference between the claimed cell line and that disclosed in Sims et al, Sims et al clearly anticipates the claimed invention.

Claims 33 and 34 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kono et al (1995) Experimental Cell Res. 221, 478-485.

Claims 33 and 34 are drawn to differentiated cells and human cells made by a claimed process. However, as a product by process claim, a teaching of the same product by a different method serves as anticipatory art.

Kono teaches differentiated hepatocytes from normal human tissue (page 479, col. 1, parag. 2, lines 1-4). Claims 33 and 34 do not distinguish from the hepatocytes taught by Kono. Without a distinction which indicates a structural or functional difference between the claimed differentiated cells and those taught by Kono, Kono clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sims et al (1993) Proced, Natl. Acad. Sci. 90, 6143-6147 in view of Lovell-Badge et al, Cold Spring Harbor Symp. Quant. Biol, Vol. 50, pages 707-711, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1985.

Claim 30 is drawn to a transgenic CICM cell line.

Sims et al teach the culture of ICM cells as cell lines 6-10 (page 6146, col. 1, parag. 2 and table 4). However, Sims does not teach a transgenic CICM cell line. Lovell-Badge teaches mouse embryonic stem cells which have been transformed with a DNA sequence encoding human type II collagen gene (page 708, col. 2, parag. 3, lines 1-4). Motivation is provided by Sims et al stating that embryonic stem cells are derived from ICM cells, and that transgenic embryonic stem cells would be advantageous for the production of cattle(page 6146, col. 2, parag. 6, line 4 to page 6147, line 2). Thus, it would have been obvious to the ordinary artisan at the time of the instant invention to produce a transgenic CICM cell line for use in the production of transgenic non-human mammals.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800

Dr. D. Crouch
December 30, 1997